The effect of caffeine on endurance performance after nonselective β-adrenergic blockade

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ABSTRACT

VAN BAAK, M. A. and W. H. M. SARIS. The effect of caffeine on endurance performance after nonselective β-adrenergic blockade. *Med. Sci. Sports Exerc.*, Vol. 32, No. 2, pp. 499–503, 2000. **Purpose:** This study was designed to test the hypothesis that combined administration of propranolol and caffeine (Pr+C) would increase endurance performance compared with the administration of propranolol alone (Pr) if caffeine would be able to increase plasma free fatty acid (FFA) availability and/or lower plasma potassium concentration compared with propranolol administration alone. **Methods:** Fifteen volunteers participated in the double-blind placebo-controlled randomized cross-over study. An endurance exercise test until exhaustion was performed after ingestion of placebo (Pl), 80-mg propranolol (Pr), and 80-mg propranolol plus 5 mg·kg^{-1} caffeine (Pr+C). **Results:** Endurance time (±SD) was 79.3 ± 20.4 min in the Pl trial, 22.6 ± 10.8 min in the Pr trial and 31.2 ± 17.2 min in the Pr+C trial ($P < 0.001$). The difference between the Pr and Pr+C trials just failed to reach statistical significance ($P = 0.056$). Plasma FFA concentration and plasma potassium concentrations were similar in the Pr and Pr+C trials, but differed significantly from the Pl trial ($P < 0.05$). **Conclusion:** Although there was a clear tendency for an improved performance in the Pr+C trial compared to the Pr trial, this improvement was not associated with increased plasma FFA concentration and/or reduced plasma potassium concentration in the Pr+C compared to the Pr trial. These results do not support the hypothesis that caffeine improves endurance performance by stimulating lipolysis or lowering plasma potassium concentration. **Key Words:** HUMAN, EXERCISE, POTASSIUM, FREE FATTY ACIDS

β-Adrenergic receptor blocking agents are drugs that are used very frequently for the treatment of cardiovascular disorders, such as hypertension and ischemic heart disease. They inhibit the effects of sympathetic nervous system activity that are mediated by the β-adrenergic receptors. During exercise the activity of the sympathetic nervous system is increased in order to create the hemodynamic and metabolic conditions necessary to provide the active muscles with the energy needed for contraction. β-Adrenergic receptor blocking agents can therefore be expected to affect the hemodynamic and metabolic adaptations during exercise. The most pronounced hemodynamic effects of β-adrenergic blockade during exercise are a reduction of heart rate, cardiac output, and arterial blood pressure (12,20). The most obvious metabolic effect is the inhibition of lipolysis in adipocytes (1,11,20,24) and possibly also in skeletal muscle (3). In addition, potassium homeostasis is affected, resulting in increased plasma potassium concentrations during exercise (8,20). The effects of β-adrenergic blockade on exercise performance are quite evident. Maximal aerobic power and maximal oxygen consumption are reduced up to 20% (20). The most pronounced effects, however, are seen during prolonged exercise. Endurance time of prolonged exercise at work loads of 60–80% $\dot{V}O_{2max}$ can be reduced more than 50% (20,22,23), depending on the type and dose of β-adrenergic blocking agent studied. This reduced performance is accompanied by an increased subjective perception of exertion. The mechanism of the reduced performance is not clear, although inhibition of lipolysis is often considered to be important (3,11,15,21). An alternative explanation is the effect of β-adrenergic blockade on potassium homeostasis (20).

Caffeine is consumed regularly by many people all over the world in the form of caffeine-containing beverages and foods. At the dosages used by humans, caffeine probably acts predominantly as an antagonist of the adenosine receptor (13,18). In contrast to β-adrenergic blocking agents, caffeine has been shown to increase endurance performance (6,9,14,17,18). It also stimulates lipolysis (4,14,17), which may be explained by its antagonistic action on the adenosine A_1 receptor in fat cells (18). An alternative or additional explanation may be the increase in catecholamine concentration that is induced by caffeine, which could also stimulate lipolysis (6,7,13). There is also evidence that caffeine stimulates sodium-potassium pump activity, thereby lowering plasma potassium concentrations, either by a direct effect or indirectly via increased catecholamine levels (10,18). The mechanism of action of caffeine with

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respect to the increase in endurance performance is not fully clear, but increased availability of free fatty acids for oxidation, thus sparing glycogen, and/or the lowering of plasma potassium levels have been suggested (4,6,10,13,18).

The present study was designed to test the following hypotheses: 1) if the lipolytic effect of caffeine is due to adrenaline stimulation, it should be blocked by administration of a β-adrenergic antagonist; if, on the other hand, it is due to direct antagonism of the adipocyte adenosine receptor, stimulation of lipolysis by caffeine should occur despite β-adrenergic blockade; 2) if the effect of caffeine on plasma potassium levels is due to adrenaline stimulation, it should be blocked by administration of a β-adrenergic antagonist; if, on the other hand, it is due to a direct effect on the Na^+-K^+-ATPase, decreases in plasma potassium concentration should occur after caffeine ingestion despite β-adrenergic blockade; 3) if availability of free fatty acids plays a key role in both the impairment of endurance performance after β-blockade and the increase in endurance performance after caffeine ingestion, endurance performance should only improve after simultaneous administration of a β-blocker and caffeine compared with β-blocker administration alone if caffeine is able to stimulate lipolysis under these conditions; 4) if potassium homeostasis plays a key role in both the impairment of endurance performance after β-blockade and the increase in endurance performance after caffeine ingestion, endurance performance should only increase after simultaneous administration of a β-blocker and caffeine compared with β-blocker administration alone if caffeine is able to lower plasma potassium concentrations under these conditions.

METHODS

Subjects. Fifteen young, healthy, male volunteers were recruited for this study. They were all well-trained in endurance sports (runners and cyclists) and exercised at least three times per week. Mean (±SD) age was 24.8 ± 5.6 yr, height 183.1 ± 5.3 cm, body mass 72.7 ± 6.1 kg, and maximal aerobic power was 5.0 ± 0.4 W/kg. The subjects were informed about the aim of the study and its possible risks, and all subjects gave written informed consent entering the study. The study was approved by the Ethics Committee of the University Hospital Maastricht and Maastricht University.

Study design. The study had a double-blind placebo-controlled randomized cross-over design. First, a progressive maximal exercise test on an electromagnetically braked cycle ergometer (Lode Excalibur, Groningen, The Netherlands) was performed to determine each individual's maximal aerobic power (Wmax). After a 5-min warm-up period at 100 W, work load was increased every 2.5 min by 50 W. When heart rate was > 160 beats·min^{-1}, the work load was increased by 25 W per 2.5 min until exhaustion. Wmax was defined as the highest work rate that could be maintained for at least 1 min.

Subsequently, each subject performed three endurance tests until exhaustion on the cycle ergometer at 70% Wmax with at least 7 d in between each tests. All tests were performed between 13:30 and 18:00 h. Room temperature was kept between 19 and 21°C. Diet and exercise was standardized on the 2 days before the endurance tests by having the subjects complete a 2-d diet and exercise log before the first test and asking them to keep as close as possible to this diary on the 2 days before the other two tests. Heavy or unusual exercise was not allowed on the day before the tests and on the test day. In addition, subjects had to refrain from caffeine containing products, such as coffee, tea, chocolate, cola, etc., during the same period. On the day of the test, no smoking was allowed. Food intake was allowed until 2 h before the start of the test. After this, only water intake was allowed. Two hours before the start of the exercise test, subjects ingested two capsules containing either placebo or propranolol (80 mg) or propranolol (80 mg) plus caffeine (5 mg·kg^{-1} body weight). The order of the medications was randomized. After subjects' arrival in the lab, a catheter for blood sampling was inserted in a forearm vein. The endurance test started with a 6-min warm-up period (3 min at 30% Wmax, 3 min at 50% Wmax). Thereafter, workload was increased to 70% Wmax and subjects cycled until exhaustion. This was defined as the moment the subjects was no longer able to maintain a pedaling rate above 50 revolutions per minute. Strong verbal encouragement was given to all subjects to cycle as long as possible. During the test subjects were allowed to drink water *ad libitum*. At regular time intervals during exercise and during the recovery from exercise, heart rate and perceived exertion were measured and blood was sampled from a forearm vein.

Methods

Heart rate was monitored by means of a telemetric device (PE 3000, Polar Electro, Kempele, Finland). The Borg scale was used to measure perceived exertion.

Blood samples were transferred to EDTA containing 1.5-mL microtest tubes and centrifuged immediately at high speed (Eppendorf centrifuge, Hamburg, Germany). Plasma was transferred to another microtest tube, frozen rapidly in liquid nitrogen and stored at −50°C until further analysis. Plasma free fatty acid concentration was determined using the Wako C test kit (Wako Chemicals, Neuss, Germany) on a Cobas-Fara centrifugal spectrophotometer (Roche, Basel, Switzerland). Plasma potassium concentration was determined by flame photometry (model 243, Instrumentation Laboratory, Lexington, MA). In all analyses, plasma samples with known concentrations were included for quality control.

Data analysis. All data are presented as mean ± SD. Differences among the three trials were analyzed with repeated measurements ANOVA. The difference between the propranolol (Pr) trial and the propranolol plus caffeine (Pr+C) trial was analyzed by means of paired Student's *t*-tests. $P < 0.05$ was regarded as statistically significant.

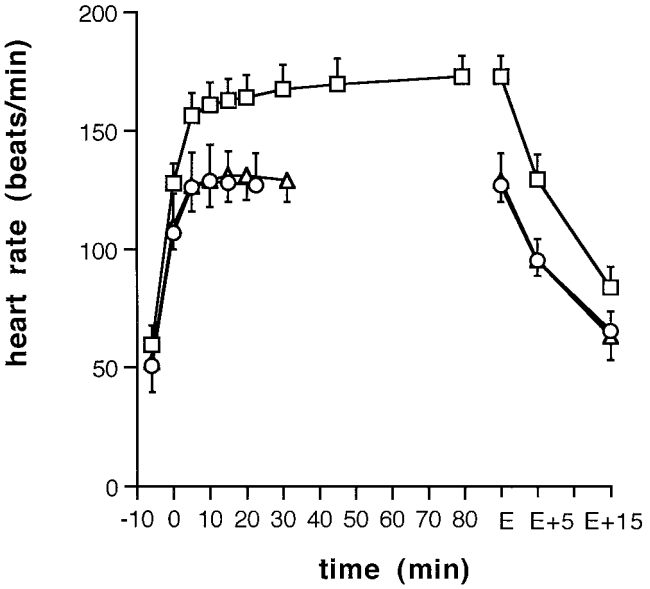

Figure 1—Heart rate (mean ± SD) during the placebo (*squares*), propranolol (*circles*), and propranolol+caffeine (*triangles*) trials (N = 15). E = moment of exhaustion, E+5 and E+15 = 5 and 15 min recovery; respectively.

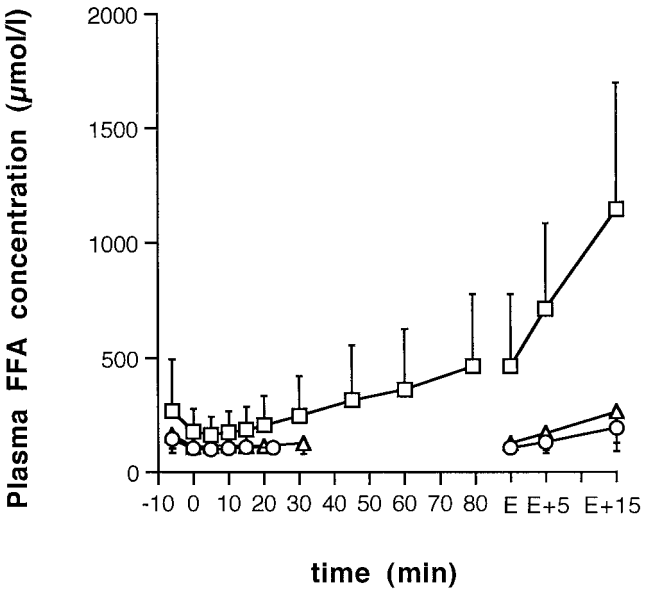

Figure 2—Plasma free fatty acid concentration (mean ± SD) during the placebo (*squares*), propranolol (*circles*), and propranolol+caffeine (*triangles*) trials (N = 15). E = moment of exhaustion, E+5 and E+15 = 5 and 15 min recovery, respectively.

RESULTS

Heart rate was significantly ($P < 0.001$) reduced in all subjects during the propranolol (Pr) and the propranolol plus caffeine (Pr+C) trials as compared with the placebo (Pl) trial (Fig. 1). No difference in heart rate was found between the Pr and Pr+C trials. At 10 min, exercise heart rate was 160.8 ± 9.6 beats·min^{-1} min during Pl, 128.9 ± 15.3 beats·min^{-1} during Pr and 129.2 ± 11.1 beats·min^{-1} during Pr+C.

The mean endurance time in all 15 subjects was 79.3 ± 20.4 min in the placebo (Pl) trial, 22.6 ± 10.8 min in the propranolol (Pr) trial, and 31.2 ± 17.2 min in the propranolol plus caffeine (Pr+C) trial ($P < 0.001$). During the Pl trial, endurance times ranged from 51 to 105 min. During the Pr and Pr+C trials, endurance time was reduced in all subjects in comparison with the Pl trial. The difference in endurance time between the Pr and the Pr+C trials just failed to reach statistical significance ($P = 0.056$): 11 of the 15 subjects improved their performance in the Pr+C trial in comparison with the Pr trial, in two it was almost unchanged, and in three it was reduced further.

The rating of perceived exertion at 10 min exercise was 11.4 ± 2.1 in the Pl trial, 15.7 ± 2.0 in the Pr trial, and 13.9 ± 2.7 in the Pr+C trial ($P < 0.001$). The difference between the Pr and the Pr+C trial was statistically significant ($P = 0.05$).

During and after exercise, plasma free fatty acid concentration was significantly lower during the Pr and Pr+C trials than during the Pl trial ($P < 0.05$) (Fig. 2). The difference between the Pr and Pr+C trials was not statistically significant. During exercise the plasma potassium concentration was significantly higher in the Pr and Pr+C trials than in the Pl trial ($P < 0.001$), but the difference rapidly disappeared during recovery (Fig. 3). There was no difference in potassium concentration between the Pr and the Pr+C trial.

DISCUSSION

At the start of the study we hypothesized that combined administration of caffeine and propranolol (Pr+C) would increase endurance performance compared with the administration of propranolol alone (Pr) if caffeine would be able to increase plasma free fatty acid availability and/or lower plasma potassium concentration compared with propranolol administration alone. Despite the fact that addition of caffeine did not change the plasma free fatty acid or potassium concentrations during endurance exercise compared with propranolol ingestion alone, there was a clear tendency for an improvement of endurance performance in the Pr+C trial compared with the Pr trial. This suggests that the ergogenic effect of caffeine during endurance exercise is not related to its effects on lipolysis or potassium homeostasis during prolonged exercise. Moreover, the increase in FFA concentration (4,14,17) and decrease in potassium concentration (10) during exercise that have been found after caffeine ingestion appear to be due to increased catecholaminergic stimulation of lipolysis and Na^+-K^+-ATPase activity, because both effects were completely prevented by simultaneous propranolol administration.

β-Adrenergic receptor blocking agents are known to impair endurance exercise performance quite dramatically. This is especially true for the nonselective β-blocking agents that block both β_1- and β_2-adrenergic receptors, where reductions of endurance time up to 54% have been found (20,22). A pronounced reduction of endurance time in the trials where propranolol, a nonselective β-blocker, was given was therefore to be expected in this study. The

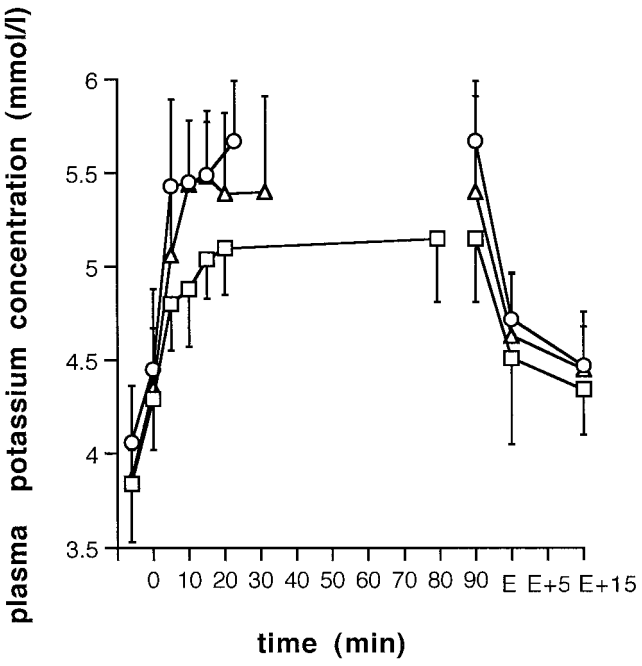

Figure 3—Plasma potassium concentration (mean ± SD) during the placebo (*squares*), propranolol (*circles*), and propranolol+caffeine (*triangles*) trials (N = 15). E = moment of exhaustion, E+5 and E+15 = 5 and 15 min recovery, respectively.

magnitude of the impairment (70 ± 15% in the Pr trial), however, was larger than in our previous studies with the same dose of propranolol (80 mg) and the same exercise test (40% (21), 51% (22), and 54% (23)). The heart rate reduction after propranolol ingestion, which is due to blockade of the cardiac β-adrenergic receptors, was slightly smaller in this (Δheart rate 32 beats·min^{-1}) than in previous studies (Δheart rate 41, 43, and 43 beats·min^{-1} (21–23)), indicating that the more pronounced impairment of endurance performance in this study can not be explained by a higher level of β-blockade. We can only speculate about the reason for this difference, but maybe the better training status of the subjects in this study plays a role. As in previous studies with nonselective β-blocker administration, plasma free fatty acid concentrations during and especially after exercise were significantly reduced, indicating inhibition of β_1- and β_2-adrenergic receptor mediated adipose tissue lipolysis (1,20,24). Plasma potassium concentrations were increased during exercise after β-blockade, which is probably due to inhibition of the β_2-adrenergic receptor stimulated sodium-potassium pump (2,8,20).

The mechanism of the pronounced reduction in endurance performance during β-blockade has, surprisingly in view of the magnitude of the effect, not yet been elucidated. One of the hypotheses is that β-blockade reduces the availability of free fatty acids for oxidation by inhibition of lipolysis. As a consequence, oxidation of carbohydrates increases and glycogen is depleted more rapidly, thus impairing endurance performance. In support of this hypothesis are the reduced plasma free fatty acid concentrations, the reduced breakdown of intramuscular triglycerides (3), and the often increased respiratory exchange ratio (20), but other findings do not support this assumption. For instance, muscle glycogen depletion does not seem to be more rapid, and skeletal muscle free fatty acid uptake is not severely impaired during exercise after β-blocker ingestion (3,5,15,23). The other hypothesis is that the disturbance of potassium homeostasis after β-blocker ingestion is responsible for the impaired performance. By altering the activity of the sodium-potassium pump, β-blockade may effect changes in plasma [K^+] and muscle excitability, which may be associated with fatigue (16,19).

To shed some more light on this discussion we designed the present study in which we combined the administration of propranolol with the ingestion of caffeine. Caffeine has been shown to increase endurance exercise performance, to increase lipolysis, and to decrease plasma potassium concentrations. Caffeine thus has exactly the opposite effects on these parameters as propranolol. This is not unexpected because the mechanisms of action of caffeine, adenosine antagonism in peripheral tissues, and increased catecholamine, especially epinephrine, production lead to an increase in cAMP production, whereas β-blockade reduces cAMP production. Before the start of the study, we hypothesized that combined administration of caffeine and propranolol would lead to an improvement of endurance performance compared with propranolol alone, if caffeine would be able to stimulate lipolysis under conditions of β-blockade. If the stimulation of lipolysis by caffeine was predominantly due to the increase in epinephrine levels after caffeine, this increase would be prevented by simultaneous β-blocker administration. On the other hand, if the increased lipolysis and/or reduced plasma [K^+] were due to adenosine antagonism, they might still be present in the presence of blockade of the β-receptors by propranolol. In our study, we found no difference in the plasma free fatty acid or potassium concentrations during the Pr and the Pr+C trials. This suggests that the effects of caffeine on lipolysis and potassium homeostasis are predominantly due to the caffeine-mediated increase in catecholamine concentrations and are thus inhibited by simultaneous propranolol ingestion. As indicated above, if a reduced availability of free fatty acids and/or increased plasma potassium concentrations are central in the performance reducing effect of β-blockade, we expected to find no increase in endurance performance due to the addition of caffeine because caffeine did not affect plasma free fatty acids or potassium concentrations under these conditions. In contrast, we did see a very strong tendency, just not statistically significant (P = 0.06), for an improvement of endurance performance by caffeine. An enhancing effect of caffeine on performance during β-blockade was supported by the lower perceived exertion during the Pr+C trial compared with the Pr trial, which is in our hands is the best predictor of endurance performance of all variables measured in this type of test (unpublished observations). These results do not support the hypothesis that caffeine improves endurance performance by stimulating lipolysis, thus increasing the free fatty acid availability for energy production and thereby delaying glycogen depletion and fatigue. Neither can changes in plasma potassium

concentration explain the effect of caffeine on performance. Graham and Spriet (7) in their study also provided evidence that the performance enhancing effect of caffeine was unrelated to its catecholamine-stimulating effect.

In conclusion, although it is evident that propranolol and caffeine both have pronounced and opposite metabolic effects, these metabolic effects do not appear to be able to explain the pronounced and opposite effects of propranolol and caffeine on endurance performance.

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